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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DIAGNOSTIC METHODS FOR THE PREDICTION OF THERAPEUTIC SUCCESS, RECURRENCE FREE AND OVERALL SURVIVAL IN CANCER THERAPY

(57) Abstract: Described are 12 human genes which are differentially expressed in neoplastic tissues of patients responding well to treatment as compared to patients not responding well as determined by overall survival time in the non responding cohort. Moreover, methods for prognosis of the therapeutic success in cancer therapy are described. These methods are based on determination of expression levels of particular genes which are differentially expressed in cancer patients, preferably the genes encoding VEGFC, ERBB3 and Her2/neu, prior to the onset of anti-cancer chemotherapy. These methods are particularly useful in the investigation of advanced head and neck cancer, but are useful in the investigation of other types of cancer and therapies as well.

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# INTERNATIONAL SEARCH REPORT

International application No <b>PCT/US2006/028180</b>
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**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. C12Q1/68 A61K39/395 C12N15/11

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
**C12Q A61K C12N**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**EPO-Internal, BIOSIS, Sequence Search, EMBASE, WPI Data**

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
<b>A</b>	<p><b>RODRIGUEZ-PINILLA MARIA ET AL: "Cyclin A as a predictive factor for chemotherapy response in advanced head and neck cancer."</b>  <b>CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 15 DEC 2004,</b>                      vol. 10, no. 24,                      15 December 2004 (2004-12-15), pages                      8486-8492, XP002427050                      ISSN: 1078-0432                      abstract</p> <p style="text-align: center;">-----                      -/--</p>	<b>1-14</b>

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

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|---|---|
| <ul style="list-style-type: none"> <li>*A* document defining the general state of the art which is not considered to be of particular relevance</li> <li>*E* earlier document but published on or after the international filing date</li> <li>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</li> <li>*O* document referring to an oral disclosure, use, exhibition or other means</li> <li>*P* document published prior to the international filing date but later than the priority date claimed</li> </ul> | <ul style="list-style-type: none"> <li>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</li> <li>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</li> <li>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</li> <li>*&amp;* document member of the same patent family</li> </ul> |
|---|---|

Date of the actual completion of the international search

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**15/06/2007**

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**Knudsen, Henrik**



## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/028180

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	O-CHAROENRAT P ET AL: "Expression of vascular endothelial growth factor family members in head and neck squamous cell carcinoma correlates with lymph node metastasis." CANCER 1 AUG 2001, vol. 92, no. 3, 1 August 2001 (2001-08-01), pages 556-568, XP002427053 ISSN: 0008-543X abstract	1-11
Y	KYZAS PANAYIOTIS A ET AL: "COX-2 expression correlates with VEGF-C and lymph node metastases in patients with head and neck squamous cell carcinoma." MODERN PATHOLOGY : AN OFFICIAL JOURNAL OF THE UNITED STATES AND CANADIAN ACADEMY OF PATHOLOGY, INC JAN 2005, vol. 18, no. 1, January 2005 (2005-01), pages 153-160, XP002427054 ISSN: 0893-3952 abstract	1-11
Y	NEUCHRIST CSILLA ET AL: "Vascular endothelial growth factor C and vascular endothelial growth factor receptor 3 expression in squamous cell carcinomas of the head and neck." HEAD & NECK JUN 2003, vol. 25, no. 6, June 2003 (2003-06), pages 464-474, XP009081449 ISSN: 1043-3074 abstract	1-11
X	WO 01/52904 A2 (GILL PARKASH S [US]; MASOOD RIZWAN [US]) 26 July 2001 (2001-07-26) page 15, paragraph 4; table 3	13,14
X	WO 00/62063 A (NORTHWEST BIOTHERAPEUTICS INC [US]; SU SAI L [US]) 19 October 2000 (2000-10-19) example 6.4	13,14
X	WO 02/057299 A2 (LUDWIG INST CANCER RES [CH]; LICENTIA LTD [FI]; ALITALO KARI [FI]; KOI) 25 July 2002 (2002-07-25) abstract	13,14
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2006/028180

## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WENNERBERG J: "Predicting response to therapy of squamous cell carcinoma of the head and neck (review)." ANTICANCER RESEARCH 1996 JUL-AUG, vol. 16, no. 4C, July 1996 (1996-07), pages 2389-2396, XP009081408 ISSN: 0250-7005 page 2391, left-hand column	7,8
P,A	EP 1 679 379 A (UMC UTRECHT HOLDING B V [NL]) 12 July 2006 (2006-07-12) abstract	1-12

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2006/028180

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-12 (partially), 13-14 (fully)

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

## 1. claims: 1-12 (partially), 13-14 (fully)

A method of predicting therapeutic success of a given mode of treatment in patient having cancer in which the expression of VEGF-C and optionally other genes is measured, the use of this method for selecting a therapy modality, a kit for carrying out the said method wherein the kit contains three primer pairs, three probes or three antibodies specific for VEGF-C, ERBB3 and Her2/neu and use of antagonists of VEGF-C in the treatment of cancer.

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## 2. claims: 1-11 (partially)

A method of predicting therapeutic success of a given mode of treatment in patient having cancer in which the expression of EGFR and optionally other genes is measured, the use of this method for selecting a therapy modality.

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## 3. claims: 1-12 (partially)

A method of predicting therapeutic success of a given mode of treatment in patient having cancer in which the expression of Her2/neu and optionally other genes is measured, the use of this method for selecting a therapy modality, a kit for carrying out the said method wherein the kit contains three primer pairs, three probes or three antibodies specific for VEGF-C, ERBB3 and Her2/neu.

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## 4. claims: 1-12 (partially)

A method of predicting therapeutic success of a given mode of treatment in patient having cancer in which the expression of ERBB3 and optionally other genes is measured, the use of this method for selecting a therapy modality, a kit for carrying out the said method wherein the kit contains three primer pairs, three probes or three antibodies specific for VEGF-C, ERBB3 and Her2/neu.

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## 5. claims: 1-11 (partially)

A method of predicting therapeutic success of a given mode of treatment in patient having cancer in which the expression of marker gene no. 5, ie ERBB4, and optionally other genes is measured, the use of this method for selecting a therapy modality.

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Inventions 6-12: Claims 1-11 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

each invention concern a method of predicting therapeutic success of a given mode of treatment in patient having cancer in which the expression of one of the marker genes 6-12 of Table 1 is measured and the use of this method in selecting a therapy modality.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2006/028180
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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